(19) Europäisch s Patentamt
Eur pean Patent Office
Office europ´en des br vets

(11) Publication numb r: **0 080 879**
B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **01.10.86**

(51) Int. Cl.⁴: **A 61 K 45/02**, A 61 K 9/00

(21) Application number: **82306319.3**

(22) Date of filing: **26.11.82**

(54) Pharmaceutical composition containing interferon in stable state.

(30) Priority: **28.11.81 JP 191250/81**
28.11.81 JP 191251/81
28.11.81 JP 191252/81
28.11.81 JP 191253/81
27.03.82 JP 49444/82

(43) Date of publication of application:
08.06.83 Bulletin 83/23

(45) Publication of the grant of the patent:
01.10.86 Bulletin 86/40

(84) Designated Contracting States:
CH DE FR GB IT LI NL SE

(56) References cited:
JP-A-55 102 519
US-A-3 981 991
US-A-4 100 150
US-A-4 137 307
US-A-4 252 791

The file contains technical information submitted after the application was filed and not included in this specification

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Descripti n

The present invention r lat s to a pharmaceutical composition containing interferon in a stable state.

It has been known that interferon is a certain kind of protein having anti-virus activity produced by stimulation of animal cells with viruses, double-stranded ribonucleic acids (RNA), etc. and has animal species specificity in its activity.

Recently, it has become apparent that interferon derived from human cells or human interferon gene-recombining microbial cells shows therapeutic effects on various human diseases and clinical application thereof has been tried.

In view of the therapeutic effects of interferon, it has been expected that interferon can be used as an active ingredient of various drugs. However, interferon is a fairly unstable material and, particularly, the activity of clinically applicable refined interferon readily decreases and this interferon is readily inactivated by elevated temperatures, mechanical treatment such as shaking, freezing or filtration and the like. Therefore, even if interferon is formulated in a composition, interferon can hardly exert its effect unless stabilization thereof is effected.

In Archives of Virology *57*, 185—188 (1978) (J. W. Heine et al) the dihydric ethylene glycol was proposed as a stabiliser for interferon.

In order to obtain a pharmaceutical composition containing human interferon in a stable state, the present inventors have intensively studied and have surprisingly found that, when a certain kind of materials is present in a composition, stability of human interferon is remarkably improved.

The main object of the present invention is to provide a pharmaceutical composition containing as an active ingredient human interferon in a stable state.

This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following decription.

According to the present invention, there is provided a pharmaceutical composition containing interferon in a stable state which comprises an effective amount of human interferon, a 15 to 60% by weight of tri or higher polyhydric sugar alcohol as a stabilizer, and a conventional pharmaceutical carrier or diluent. Optionally, in addition to the sugar alcohol, the composition of the present invention can further contain as a stabilizer a material selected from acidic sugars and salts thereof, organic acid buffers, sulfur-containing mild reducing agents having sulfhydryl group selectivity, anionic surfactants and combinations thereof. The composition of the present invention can be prepared in various forms suitable for application in the oral cavity, topical application to the skin, rectal, vaginal and urethral administration, application to the eye, the ear, the nose and the throat and the interferon in the composition can maintain its activity for a long period of time.

Interferon to be formulated in the composition of the present invention can be any interferon derived from human being. For example, there can be used interferon prepared by using human leukocytes or normal human diploid cells according to a known technique, interferon derived from human interferon gene-recombining microbial cells prepared according to a known recombination deoxyribonucleic acid (DNA) technique or interferon prepared by using a known cell-fusion technique. The amount of interferon to be formulated in the composition is not limited to a specific one and can be appropriately chosen based on a desired effect, a particular form of the composition and the like. However, generally, in view of the effect, it is preferable to formulate interferon having the specific activity of 1×10^5 international units (IU)/mg protein or more in an amount of 1×10^4 IU or more per 100 g of the composition.

Examples of the polyhydric sugar alcohols to be used as the stabilizer in the present invention are those of trihydric or higher such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol. These polyhydric sugar alcohols can be used alone or in a combination thereof. As mentioned above, the sugar alcohol is formulated in an amount of 15 to 60% by weight, preferably, 25 to 60% by weight, based on the composition.

Examples of the acidic sugars and salts thereof are iduronic acid, galacturonic acid, glucuronic acid, gulonic acid, mannuronic acid, ketogluconic acid, ketogalactonic acid, ketogulonic acid, ascorbic acid and salts thereof with alkali metals such as sodium and potassium. These acidic sugars can be used alone or in a combination thereof. In view of stabilization of interferon, the acidic sugar is formulated in an amount of at least 0.01% by weight, preferably, 0.1 to 1% by weight based on the composition.

The organic acid buffers to be used as the stabilizer in the present invention can be conventional buffers of organic acids and salts thereof such as citrate buffers (e.g. monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture), succinate buffers (e.g. succinic acid-monosodium succinate mixture, succinic acid-sodium hydroxide mixture, succinic acid-disodium succinate mixture), tartrate buffers (e.g. tartaric acid-sodium tartrate mixture, tartaric acid-potassium tartrate mixture, tartaric acid-sodium hydroxide mixture), fumarate buffers (e.g. fumaric acid-monosodium fumarate mixture, fumaric acid-disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture), gluconate buffers (e.g. gluconic acid-sodium gluconate mixture, gluconic acid-sodium hydroxide mixtur , gluconic acid-potassium gluconate mixture), oxalate buffers (e.g. oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture), lactate buffers (e.g. lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture) and acetate buffers (e.g. acetic acid-sodium acetate mixture, acetic

acid-sodium hydroxide mixture). It is noteworthy that inorganic acid buffers such as phosphate buffers do not improve the stability of interferon. The organic acid buffer is formulated in an amount of 0.01 mole/kg composition or more, preferably, 0.1 to 0.2 mole/kg composition so as to adjust to pH 3 to 6.

Examples of the sulfur-containing mild reducing agents having sulfhydryl group selectivity are thioctic acid, N-acetylcysteine, N-acetylhomocysteine, glutathione, thiodiglycollic acid, thioethanolamine, monothioglycerol, dithiothreitol and thioalkanoic acids having 1 to 7 carbon atoms. These reducing agents can be used alone or in a combination thereof and are formulated in an amount of 0.001% by weight or more, preferably, 0.01 to 0.1% by weight based on the composition.

Examples of the anionic surfactants are sodium alkyl sulfates, alkyl groups of which have 8 to 18 carbon atoms (e.g. sodium lauryl sulfate, sodium oleyl sulfate) sodium polyoxyethylene alkyl ether sulfates, average number of moles of ethylene oxide added of which are 2 to 4 and alkyl groups of which have 8 to 18 carbon atoms (e.g. sodium polyoxyethylene lauryl ether sulfate, sodium polyoxyethylene oleyl ether sulfate) and sodium alkyl sulfosuccinates alkyl groups of which have 8 to 18 carbon atoms (e.g. sodium lauryl sulfosuccinate, sodium oleyl sulfosuccinate). It is noteworthy that, among various surfactants, only anionic surfactants can improve the stability of interferon. The anionic surfactants can be used alone or in a combination thereof and are formulated in an amount of 0.008% by weight or more, preferably, 0.05% to 4% by weight or more, particularly, 0.1 to 1% by weight based on the composition.

In the present invention, as mentioned above, the polyhydric sugar alcohol can be used alone or it can be used in a combination thereof with one or more the other stabilizers set forth in the above.

The pharmaceutical carrier or diluent to be used in the present invention can be solid or liquid. For example, there can be used waxes, cellulose derivatives, carboxyvinyl polymers and water.

The composition of the present invention can be prepared in a conventional form known in the fields of drugs such as pasta (a form of paste) and gargle for application in the oral cavity, gel and ointment for topical application to the skin, gel and suppository for rectal, vaginal and urethral administration and liquid, gel, ointment and spray for application to the eye, the ear, the nose and the throat by incorporating the stabilizer and the carrier or diluent with interferon according to a conventional technique. In order to avoid a decrease of the activity of interferon during the manufacturing steps, it is preferable to add interferon to a mixture of remaining ingredients at the end step.

The other ingredient(s) are not specified unless they affect on the activity of interferon and conventional ingredients such as perfumes or sweeteners can be used.

The following Experiments and Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof. Interferon used in the Experiments and Examples was obtained from fibroblasts derived from human prepuce by the superinduction method (Tan, Y. H., Armstrong, J. A., Ke, Y. H. and Ho, M. (1970), Proc. Natl. Acad. Sci., 67, 464; and Vilcêk, J. (1970), J. Gen. Viol., 56, 76). The activity of interferon was measured by using Sindbis virus and a cell line derived from human amnion (FL cells) according to the cytopathogenic effect (CPE) method (Havell, E. A. and Vilcek, J. (1972), Antimicrob, Agents Chemother., *2*, 476; Oie, H. K., (1977), Texas Rep. Biol. Med., *35*, 154). The activity thus measured was compared with that of standard interferon measured at the same time and was expressed in international units (IU).

Experiment 1

Lyophilized interferon (1×10^6 IU) was restored by adding a physiological saline solution (1 ml) and was diluted with a physiological saline solution to obtain an interferon solution (1×10^5 IU/ml). The interferon solution (0.1 ml) was mixed with physiological saline solution (0.9 ml) containing the sugar alcohol shown in Table 1 and allowed to stand at 45°C for 24 hours. After 24 hours, the activity of interferon in the mixture was measured and the rate of remaining activity (%) was calculated by taking the initial activity as 100%. The results as well as the sugar alcohols used and the concentration thereof are shown in Table 1.

TABLE 1

Sugar alcohols	Concentrations (wt.%)	Rate of remaining activity (%)
Glycerin	45	100
Glycerin	27	17
Glycerin	10	8
Glycerin	2	7
Xylitol	45	70
Sorbitol	45	30
Mannitol	45	50
Erythritol	45	88
Control (without addition of any sugar alcohol)	—	0

Experiment 2

The same procedure as described in Experiment 1 was repeated except that the mixture was allowed to stand at 37°C for 1 month or 4°C for 6 months. The results are shown in Table 2.

TABLE 2

Sugar alcohols	Concentrations (wt.%)	Rate of remaining activity (%)	
		37°C, 1 month	4°C, 6 months
Glycerin	45	80	95
Xylitol	45	60	80
Sorbitol	45	25	30
Mannitol	45	42	70
Erythritol	45	70	90
Control (without addition of any sugar alcohol)	—	0	8

As shown in Tables 1 and 2, all the sugar alcohols used, particularly, glycerin, xylitol and erythritol improve stability of interferon.

Experiment 3

The interferon solution as prepared in Experiment 1 (0.1 ml) was mixed with an aqueous solution (0.9 ml) containing the buffer shown in Table 3 and was allowed to stand with shaking (170 r.p.m.) at 37°C for 24 hours. After 24 hours, the activity of interferon in the mixture was measured and the rate of remaining activity (%) was calculated according to the same manner as in Experiment 1. The results are shown in Table 3.

TABLE 3

Buffers	Concentrations (mole/liter)	pH	Rate of r maining activity (%)
Phosphate buffer	0.1	6	4
Phosphate buffer	0.1	7	8
Phosphate buffer	0.1	8	6
Citrate buffer	0.1	4	79
Citrate buffer	0.1	5	75
Citrate buffer	0.1	6	53
Control (distilled water)	—	6	0

Experiment 4

The interferon solution as prepared in Experiment 1 (0.1 ml) was mixed with an aqueous solution (0.9 ml) containing the surfactant shown in Table 6 and was allowed to stand at 45°C for 24 hours. After 24 hours, the activity of interferon in the mixture was measured and the rate of remaining activity (%) was calculated according the same manner as in Experiment 1. The results are shown in Table 4.

TABLE 4

Surfactants	Concentrates (wt.%)	Rate of remaining activity (%)
Sodium lauryl sulfate (anionic surfactant)	1	94
	0.2	92
	0.04	52
	0.008	40
	0.0016	4
Polyoxyethylene sorbitan fatty acid ester (nonionic surfactant)*	1	7
	0.2	7
	0.04	6
Polyoxyethylene hardened castor oil derivative (nonionic (surfactant)**	1	5
	0.2	6
	0.04	5
Control (distilled water)	—	5

*: Tween® 80 manufactured by Atlas Powder Col in U.S.A.
**: Nikkol® HCO-60 manufactured by Nikko Chemical Col, Ltd. in Japan

As shown in Tabl 4, th anionic surfactants improve stability of interferon, whereas the nonionic surfactants do not improve stability of interf ron.

Example 1

According to the following formulation, various topical pastas were prepared.

Ingredients	% by weight
Cetanol	2.0
Glyceryl monostearate	9.27
Tween® 80	2.0
Hydroxyethyl cellulose	5.5
Saccharin	0.09
Sugar alcohol (shown in Table 5)	40.0
Distilled water	up to 100%

The above ingredients were mixed and to the mixture was added an interferon solution prepared as in Experiment 1 in an amount of 1×10^7 IU/100 g product. The resulting mixture was thoroughly mixed to obtain an interferon-containing dental pasta.

The dental pasta thus obtained was allowed to stand at 37°C for 1 month or at 4°C for 6 months. After this period, the activity of interferon in the pasta was measured and the rate of remaining activity (%) was calculated by taking the initial activity as 100%. The results are shown in Table 5.

TABLE 5

Sugar alcohols	Rate of remaining activity (%)	
	37°C, 1 month	4°C, 6 months
Glycerin	84	92
Erythritol	72	84
Arabitol	60	60
Mannitol	48	74
Control (substituted distilled water for sugar alcohol)	0	0

Example 2

According to the same procedure as described in Example 1, dental pastas were prepared and the rates of remaining activity (%) of interferon were calculated after storage at 37°C for 1 month and at 4°C for 6 months. The formulations and the results are shown in Table 6.

TABLE 6

Ingredients	% by weight		
	1	2	3
Sodium carboxy-methyl cellulose	2.0	2.0	2.0
Glycerin	45.0	30.0	20.0
Ascorbic acid	1.0	1.0	1.0
Distilled water	up to 100%	up to 100%	up to 100%
Interferon	1×10^7 IU/100 g product	1×10^7 IU/100 g product	1×10^7 IU/100 g product
Rate of remaining activity (%)			
37°C, 1 month	83	81	55
4°C, 6 months	95	94	75

Example 3

According to the same procedure as described in Example 1, dental pastas were prepared and the rates of remaining activity (%) of interferon were calculated after storage at 37°C for 1 month and 4°C for 6 months. The formulations and the results are shown in Table 7.

TABLE 7

Ingredients	% by weight		
	1	2	3
Sodium carboxy-methyl cellulose	2.0	2.0	2.0
Glycerin	45.0	30.0	20.0
Sodium lauryl sulfate	0.2	0.2	0.2
Citrate buffer (pH 4.5, 0.1 mole/liter distilled water)	up to 100%	up to 100%	up to 100%
Interferon	1×10^7 IU/100 g product	1×10^7 IU/100 g product	1×10^7 IU/100 g product
Rate of remaining activity (%)			
37°C, 1 month	85	82	60
4°C, 6 months	96	94	77

Example 4

According to the following formulation, a gargle was prepared.

Ingredients	% by weight
Organic acid buffer (shown in Table 8, 0.2 mole/liter distilled water; pH 4.5)	50.0
Glycerin	25.0
Saccharin	0.02
Perfume	0.02
Distilled water	up to 100%
Interferon	1×10^6 IU/100 g product

The above ingredients were mixed and to the mixture was added an interferon solution prepared as in Experiment 1 in an amount of 1×10^6 IU/100 g product. The resulting mixture was thoroughly mixed to obtain an interferon-containing gargle.

The gargle thus obtained was allowed to stand at 37°C for 1 month or at 4°C for 6 months. After this period, the remaining activity of interferon was measured and the rate of remaining activity (%) was measured by taking the initial activity as 100%.

The results are shown in Table 8.

TABLE 8

Organic buffers	Rate of remaining activity (%)	
	37°C, 1 month	4°C 6 months
Citrate buffer	58	92
Succinate buffer	55	90
Tartrate buffer	42	79
Fumarate buffer	48	72
Gluconate buffer	40	70
Oxalate buffer	50	80
Lactate buffer	56	84
Acetate buffer	60	88
Control (without buffer)	0	2

Example 5

According to the same procedure as described in Example 4, a gargle of the following formulation was prepared and the rate of remaining activity (%) of interferon was calculated after storage at 37°C for 1 month or at 4°C for 6 months.

Ingr dients	% by weight
Anionic surfactant (shown in Table 9)	0.2
Glycerin	25.0
Saccharin	0.02
Ascorbic acid	0.2
Perfume	0.02
Citrate buffer (pH 4.5, 0.1 mole/liter distilled water)	up to 100%
Interferon	1×10^6 IU/100 g product

The results are shown in Table 9.

TABLE 9

Anionic surfactants	Rate of remaining activity (%)	
	37°C, 1 month	4°C, 6 months
Sodium lauryl sulfate	78	98
Sodium lauryl sulfosuccinate	84	94
Polyoxyethylene lauryl ether sulfate	77	96
Control (substituted refined water for anionic surfactant)	0	2

Example 6

According to the following formulation, a gel for topical application to the skin was prepared by a standard technique provided that an interferon solution prepared as in Experiment 1 was added at the end step.

Ingredients	% by weight
Sugar alcohol (shown in Table 10)	45.0
Tween® 80	0.2
Carbopol® 940 (carboxyvinyl polymer manufactured by B. F. Goodrich Co. in U.S.A.)	2.0
Ascorbic acid	1.0
Distilled water	up to 100%
Interferon	1×10^7 IU/100 g product

The interferon-containing gel thus obtained was allowed to stand at 37°C for 1 month or at 4°C for 6 months. After this period, the remaining activity of interferon was measured and the rate of remaining activity (%) was calculated by taking the initial activity as 100%.

The results are shown in Table 10.

TABLE 10

Sugar alcohols	Rate of remaining activity (%)	
	37°C, 1 month	4°C, 6 months
Glycerin	80	88
Erythritol	76	80
Arabitol	70	64
Mannitol	40	76
Control (substituted distilled water for sugar alcohol)	0	1

Example 7

According to the same procedure as described in Example 6, an interferon-containing gel for topical application to the skin of the following formulation.

Ingredients	% by weight
Glycerin	45
Sodium carboxymethyl cellulose	2
Sodium lauryl sulfate	0.2
Citrate buffer (pH 4.5, 0.1 mole/liter distilled water)	up to 100%
Interferon	1×10^6 IU/100 g product

When the gel was allowed to stand at 37°C for 1 month or at 4°C for 6 months, the rate of remaining activity (%) of interferon was 70% after storage at 37°C for 1 month and 90% after storage at 4°C for 6 months. When glycerin in the above formulation was substituted for distilled water, the rate of remaining activity (%) of interferon in the resulting gel was 0% after storage at 37°C for 1 month and 1% after storage at 4°C for 6 months.

Example 8

According to the same procedure as described in Example 6, a topical gel of the following formulation was prepared and the rate of remaining activity (%) of interferon was calculated after storage at 37°C for one month or at 4°C for 6 months.

Ingredients	% by weight
Tween® 80	0.2
Carbopol® 940	2.0
Glycerin	30.0
Organic acid buffer (shown in Table 11, 0.2 mole/liter aqueous solution; the final pH was adjusted to 5.0)	up to 100%
Interferon	1×10^6 IU/100 g product

The results are shown in Table 11.

TABLE 11

Organic buffers	Rate of remaining activity (%)	
	37°C, 1 month	4°C 6 months
Citrate buffer	38	94
Succinate buffer	40	92
Tartrate buffer	42	90
Fumarate buffer	36	88
Gluconate buffer	28	80
Oxalate buffer	40	86
Lactate buffer	30	84
Acetate buffer	38	92
Control (without buffer)	0	1

Example 9

According to the same procedure as described in Example 6, a topical gel of the formulation shown in Table 12 was prepared and the rate of remaining activity (%) of interferon was calculated after storage at 37°C for 1 month or at 4°C for 6 months. The results are shown in Table 12.

TABLE 12

Ingredients	% by weight			
	1	2	3	4
Sodium lauryl sulfate	0.2	0.04	0.008	0
Glycerin	15	15	15	15
Sodium carboxy-methyl cellulose	2	2	2	2
Distilled water	up to 100%	up to 100%	up to 100%	up to 100%
Interferon	1×10^7 IU/100 g product	1×10^7 IU/100 g product	1×10^7 IU/100 g product	1×10^7 IU/100 g product
Rate of remaining activity (%)				
37°C, 1 month	94	84	54	6
4°C, 6 months	100	100	85	22

Example 10

According to the formulation shown in Table 13, an interferon-containing ointment was prepared by a standard technique provided that an interferon solution prepared as in Experiment 1 was added at the end step. The ointment was allowed to stand at 37°C for 1 month or at 4°C for 6 months. After this period, the remaining activity of interferon was measured and the rate of remaining activity (%) was calculated by taking the initial activity as 100%. The results are shown in Table 13.

TABLE 13

Ingredients	% by weight
Glycerin	30
Ascorbic acid	1.0
White petrolatum	25
Stearyl alcohol	22
Citrate buffer (pH 4.5, 0.1 mole/liter distilled water)	up to 100%
Interferon	1×10^6 IU/100 g product
Rate of remaining activity (%) 37°C, 1 month	58
4°C, 6 months	92

Example 11

The acidic sugar shown in Table 14 was added to a mixture of Macrogol® 400 (polyethylene glycol) 60 g and glycerin 40 g in a concentration of 0.05% by weight. An interferon solution prepared as in Experiment 1 was added to the mixture in an amount of 1×10^6 IU/100 g mixture and thoroughly mixed. The resulting mixture was put into a container, cooled and shaped and each 1 g portion thereof was filled into a capsule to obtain an interferon-containing suppository. The suppository thus obtained was allowed to stand at 37°C for 1 month or at 4°C for 6 months. after this period, the remaining activity of interferon was measured and the rate of remaining activity (%) of interferon was calculated by taking the initial activity as 100%. The results are shown in Table 14.

TABLE 14

Acidic sugars	Rate of remaining activity (%)	
	37°C, 1 month	4°C, 6 months
Iduronic acid	32	64
Galacturonic acid	28	62
Glucuronic acid	30	60
Gulonic acid	27	60
Mannuronic acid	40	58
Ketogluconic acid	38	52
Ketogalactonic acid	29	56
Ketogulonic acid	30	48
Ascorbic acid	48	72
Control (without acidic sugar)	0	2

Example 12

According to the same procedure as described in Example 11, an interferon-containing suppository of the following formulation was prepared and the rate of remaining activity (%) of interferon was calculated after storage at 37°C for 1 month or at 4°C for 6 months.

Ingredients	% by weight
Macrogol® 400	50
Glycerin	35
Organic acid buffer (shown in Table 15, 0.1 mole/liter aqueous solution; pH 5.0)	15
Sodium lauryl sulfate	0.2
Interferon	1×10^6 IU/g mixture

The results are shown in Table 15.

TABLE 15

Organic acid buffers	Rate of remaining activity (%)	
	37°C, 1 month	4°C 6 months
Citrate buffer	70	80
Succinate buffer	72	78
Tartrate buffer	60	70
Fumarate buffer	60	70
Gluconate buffer	53	66
Oxalate buffer	60	70
Lactate buffer	72	80
Acetate buffer	62	72
Control (macrogole)	0	4

Claims

1. A pharmaceutical composition containing interferon in a stable state which comprises an effective amount of human interferon, 15 to 60% by weight of a tri or higher polyhydric sugar alcohol as a stabilizer, and a conventional pharmaceutical carrier or diluent.

2. A composition according to claim 1, wherein the polyhydric sugar alcohol is a member selected from glycerin, erythritol, arabitol, xylitol, sorbitol, mannitol and a mixture thereof.

3. A composition according to claim 1 or claim 2 wherein the composition further includes as a stabilizer a material selected from acidic sugars and salts thereof, organic acid buffers, sulfur-containing mild reducing agents having sulfhydryl group selectivity, anionic surfactants and combinations thereof.

4. A composition according to claim 3, wherein the acidic sugar is a member selected from iduronic acid, galacturonic acid, glucuronic acid, gulonic acid, mannuronic acid, ketogluconic acid, ketogalactonic acid, ketogulonic acid, ascorbic acid, a salt thereof with alkali metals and a mixture thereof and is formulated in an amount of 0.01 to 1% by weight based on the composition.

5. A composition according to claim 3, wherein the organic acid buffer is a member selected from citrate buffer, succinate buffer, fumarate buffer, gluconate buffer, oxalate buffer, lactate buffer and acetate buffer and is formulated in an amount of 0.01 to 0.2 mole/kg composition so as to adjust pH of the composition to 3 to 6.

6. A composition according to claim 3, herein the reducing agent is a member selected from thioctic acid, N-acetylcysteine, N-acetylhomocysteine, glutathione, thiodiglycollic acid, thioethanolamine, monothioglycerol, dithiothreitol, thioalkanoic acid having 1 to 7 carbon atoms and mixture thereof and is formulated in an amount of 0.001 to 0.1% by weight based on the composition.

7. A composition according to claim 3, wherein the anionic surfactant is a member selected from sodium alkyl sulfate, the alkyl group of which has 8 to 18 carbon atoms; sodium polyoxyethylene alkyl ether sulfate, the average number of mole of ethylene oxide added of which is 2 to 4 and the alkyl group of

which has 8 to 18 carbon atoms; sodium alkyl sulfosuccinate, the alkyl group of which has 8 to 18 carbon atoms; and a mixture thereof and is formulated in an amount of 0.008 to 4% by weight based on the composition.

8. A composition according to any one of claims 3 to 7, wherein the stabilizer is a mixture of the polyhydric sugar alcohol and the acidic sugar.

9. A composition according to any one of claims 3 to 7 wherein the stabilizer is one of the following mixtures:—

the polyhydric sugar alcohol, the acidic sugar and the organic acid buffer;

the polyhydric sugar alcohol, the acidic sugar and the reducing agent; or

the polyhydric sugar alcohol, the acidic sugar and the anionic surfactant.

10. A composition according to any one of claims 3 to 7 wherein the stabilizer is a mixture of the polyhydric sugar alcohol, the acidic sugar, the organic acid buffer and the reducing agent, or

a mixture of the polyhydric sugar alcohol, the acidic sugar, the organic acid buffer and the anionic surfactant.

11. A composition according to any one of claims 3 to 7 wherein the stabilizer is a mixture of the polyhydric sugar alcohol, the acidic sugar, the organic acid buffer, the reducing agent and the anionic surfactant.

12. A composition according to any one of the preceding claims which is in the form for application in the oral cavity.

13. A composition according to any of claims 1 to 11 in the form for topical application to the skin.

14. A composition according to any of claims 1 to 11 in the form for rectal administration.

15. A composition according to any of claims 1 to 11 in the form for vaginal administration.

16. A composition according to any of claims 1 to 11 in the form for urethral administration.

17. A composition according to any of claims 1 to 11 in the form for application to the eye.

18. A composition according to any of claims 1 to 11 in the form for application to the ear.

19. A composition according to any of claims 1 to 11 in the form for application to the nose.

20. A composition according to any of claims 1 to 11 in the form for application to the throat.

21. A composition according to any one of the preceding claims wherein interferon having the specific activity of at least 1×10^5 IU/mg protein is formulated in an amount of at least 1×10^4 IU per 100 g of the composition.

Patentansprüche

1. Arzneimittel, welches Interferon in einem stabilen Zustand enthält, dadurch gekennzeichnet, daß es eine wirksame Menge von Human-Interferon, 15 bis 60 Gew.-% eines drei- oder höheren mehrwertigen Zuckeralkohols als Stabilisator, und einen herkömmlichen pharmazeutischen Träger oder Verdünnungsmittel enthält.

2. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß der mehrwertige Zuckeralkohol ein Glied, ausgewählt aus Glycerin, Erythrit, Arabit, Xylit, Sorbit, Mannit und einem Gemisch davon ist.

3. Arzneimittel nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß es weiterhin als Stabilisator ein Material, ausgewählt aus sauren Zuckern und Salzen davon, organischen Säurepuffern, Schwefel enthaltenden milden Reduktionsmitteln mit einer Selektivität für Sulfhydryl-gruppen, anionischen oberflächenaktiven Mitteln und Kombinationen davon, enthält.

4. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß der saure Zucker ein Glied, ausgewählt aus Iduronsäure, Galacturonsäure, Glucuronsäure, Guluronsäure, Mannuronsäure, Ketogluconsäure, Ketogalactonsäure, Ketogulonsäure, Ascorbinsäure, ein Salz davon mit Alkalimetallen und ein Gemisch davon, ist und in einer Menge von 0,01 bis 1 Gew.-%, bezogen auf das Arzneimittel, formuliert ist.

5. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß der organische Säurepuffer ein Glied, ausgewählt aus Citratpuffer, Succinatpuffer, Fumaratpuffer, Gluconatpuffer, Oxalatpuffer, Lactatpuffer und Acetatpuffer, ist und in einer Menge von 0,01 bis 0,2 Mol/kg Arzneimittel formuliert ist, so daß der pH-Wert des Arzneimittels auf 3 bis 6 eingestellt wird.

6. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß das Reduktionsmittel ein Glied, ausgewählt aus Thioctinsäure, N-Acetylcystein, N-Acetylhomocystein, Glutathion, Thiodiglykolsäure, Thioethanolamin, Monothioglycerin, Dithiothreit, Thioalkansäure mit 1 bis 7 Kohlenstoffatomen und Gemisch davon, ist und in einer Menge von 0,001 bis 0,1 Gew.-%, bezogen auf das Arzneimittel, formuliert ist.

7. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß das anionische oberflächenaktive Mittel ein Glied, ausgewählt aus Natriumalkylsulfat, wobei die Alkylgruppe 8 bis 18 Kohlenstoffatome besitzt, Natriumpolyoxyethylenalkylethersulfat, wobei die durchschnittliche Anzahl von moladdiertem Ethylenoxid 2 bis 4 beträgt und die Alkylgruppe 8 bis 18 Kohlenstoffatome besitzt, Natriumalkylsulfosuccinat, wobei die Alkylgruppe 8 bis 18 Kohlenstoffatome besitzt, und ein Gemisch davon, its und in einer Menge von 0,008 bis 4 Gew.-%, bezogen auf das Arzneimittel, formuliert ist.

8. Anzneimittel nach einem der Ansprüche 3 bis 7, dadurch gekennzeichnet, daß der Stabilisator ein Gemisch des mehrwertigen Zuckeralkohols und dem sauren Zucker ist.

9. Arzneimittel nach ein m der Ansprüche 3 bis 7, dadurch gekennzeichnet, daß der Stabilisator ines der folgenden Gemische ist;

der mehrw rtig Zuck ralkohol, der saure Zucker und der organische Säurepuffer,

der mehrwertige Zuckeralkohol, der saure Zucker und das Reduktionsmittel, oder

der mehrwertige Zuckeralkohol, der saure Zucker und das anionische oberflächenaktive Mittel.

10. Arzneimittel nach einem der Ansprüche 3 bis 7, dadurch gekennzeichnet, daß der Stabilisator ein Gemisch aus dem mehrwertigen Zuckeralkohol, dem sauren Zucker, dem organischen Säurepuffer und dem Reduktionsmittel, oder

ein Gemisch aus dem mehrwertigen Zuckeralkohol, dem sauren Zucker, dem organischen Säurepuffer und dem anionischen oberflächenaktiven Mittel ist.

11. Arzneimittel nach einem der Ansprüche 3 bis 7, dadurch gekennzeichnet, daß der Stabilisator ein Gemisch aus dem mehrwertigen Zuckeralkohol, dem sauren Zucker, dem organischen Säurepuffer, dem Reduktionsmittel und dem anionischen oberflächenaktiven Mittel ist.

12. Arzneimittel nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß es in einer Form für die Anwendung in der Mundhöhle vorliegt.

13. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die topische Aufbringung auf die Haut vorliegt.

14. Arzneitmittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in einer Form für die rektale Verabreichung vorliegt.

15. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die vaginale Verabreichung vorliegt.

16. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die urethrale Verabreichung vorliegt.

17. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die Anwendung in das Ange vorliegt.

18. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die Anwendung in das Ohr vorliegt.

19. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die Anwendung in die Nase vorliegt.

20. Arzneimittel nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß es in der Form für die Anwendung in die Kehle vorliegt.

21. Arzneimittel nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß Interferon mit einer spezifischen Aktivität von mindestens 1×10^5 IU/mg Protein in einer Menge von mindestens 1×10^4 IU pro 100 g des Arzneimittels formuliert ist.

Revendications

1. Une composition pharmaceutique contenant de l'interféron sous une forme stable qui comprend une quantité efficace d'interféron humain, 15 à 60% en poids d'un polyalcool à caractére glucidique trihydroxylé ou d'hydroxylation supérieure comme stabilisant, et un support ou diluant pharmaceutique classiques.

2. Une composition selon la revendication 1, dans laquelle le polyalcool à caractère glucidique est un composant choisi parmi la glycérine, l'érythritol, l'arabitol, le xylitol, le sorbitol, le mannitol et un de leurs mélanges.

3. Une composition selon la revendication 1 ou la revendication 2, dans laquelle la composition comprend de plus comme stabilisant une matière choisie parmi les sucres acides et leurs sels, les tampons acides organiques, les agents réducteurs faibles soufrés ayant une sélectivité pour le groupe sulfhydryle, les agents tensio-actifs anioniques et leurs combinaisons.

4. Une composition selon la revendication 3, dans laquelle le sucre acide est un composant choisi parmi l'acide iduronique, l'acide galacturonique, l'acide glucuronique, l'acide gulonique, l'acide mannuronique, l'acide cétogluconique, l'acide cétogalactonique, l'acide cétogulonique, l'acide ascorbique, un sel de ceux-ci formé avec les métaux alcalins et un mélange de ceux-ci, et est incorporé à raison de 0,01 à 1% en poids par rapport à la composition.

5. Une composition selon la revendication 3, dans laquelle le tampon acide organique est un composant choisi parmi un tampon citrate, un tampon succinate, un tampon fumarate, un tampon gluconate, un tampon oxalate, un tampon lactate et un tampon acétate, et est incorporé à raison de 0,01 à 0,2 mol/kg de composition de façon à ajuster le pH de la composition entre 3 et 6.

6. Une composition selon la revendication 3, dans laquelle l'agent réducteur est un composant choisi parmi l'acide thioctique, la N-acétylcystéine, la N-acétylhomocystéine, le glutathion, l'acide thiodiglycolique, la thioéthanolamine, le monothioglycérol, le dithiothréitol, un acide thioalcanoïque ayant 1 à 7 atome de carbone et leurs mélanges, et est incorporé à raison de 0,001 à 0,1% en poids par rapport à la composition.

7. Une composition selon la revendication 3, dans laquelle l'agent tensio-actif anionique est un composant choisi parmi un alkylsulfate de sodium dont le groupe alkyle a 8 à 18 atomes de carbone; un polyoxyéthylène-éther alkylique-sulfate de sodium dont le nombre moyen des moles d'oxyde d'éthylène

ajoutées est de 2 à 4 et dont le groupe alkyle a 8 à 18 atomes de carbones; un alkylsulfosuccinate de sodium dont le groupe alkyl a 8 à 18 atomes de carbone; et un de leurs mélanges, et est incorpor´ à raison de 0,008 à 4% en poids par rapport à la composition.

8. Une composition selon l'une quelconque des revendications 3 à 7, dans laquelle le stabilisant est un mélange du polyalcool à caractère glucidique et du sucre acide.

9. Une composition selon l'une quelconqu des revendications 3 à 7, dans laquelle le stabilisant est un des mélanges suivant:

le polyalcool à caractère glucidique, le sucre acide et le tampon acide organique;

le polyalcool à caractère glucidique, le sucre acide et l'agent réducteur; ou

le polyalcool à caractère glucidique, le sucre acide et l'agent tensio-actif anionique.

10. Une composition selon l'une quelconque des revendications 3 à 7, dans laquelle le stabilisant est un mélange du polyalcool à caractère glucidique, du sucre acide, du tampon acide organique et de l'agent réducteur, ou un mélange du polyalcool à caractère glucidique, du sucré acide, du tampon acide organique en de l'agent tensio-actif anionique.

11. Une composition selon l'une quelconque des revendications 3 à 7, dans laquelle le stabilisant est un mélange du polyalcool à caractère glucidique, du sucre acide, du tampon acide organique, de l'agent réducteur et de l'agent tensio-actif anionique.

12. Une composition selon l'une quelconque des revendications précédentes qui est sous une form pour l'application à la cavité buccale.

13. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'application locale à la peau.

14. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'administration rectale.

15. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'administration vaginale.

16. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'administration urétrale.

17. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'application aux yeux.

18. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'application aux oreilles.

19. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'application au nez.

20. Une composition selon l'une quelconque des revendications 1 à 11 qui est sous une forme pour l'application à la gorge.

21. Une composition selon l'une quelconque des revendications précédentes dans laquelle un interféron ayant une activité spécifique d'au moins 1×10^5 UI/mg de protéines est incorporé en une quantite d'au moins 1×10^4 UI/100 g de la composition.